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Regioselectivity and Diastereoselectivity in the Phase Transfer Catalysed Michael Addition of 2-Phenylcyclohexanone

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Abstract. Regioselectivity and diastereoselectivity in the Michael addition of 2-phenylcyclohexanone to bulky α,β-unsaturated ketones can be controlled by carefully selecting the reaction conditions. Solvent-free solid-liquid PTC using tetrabutylammonium bromide as catalyst and potassium *tert*butoxide as base leads to high *de* (up to 99%) of the 2,6-disubstituted regioisomer, which is, *a priori*, the unexpected isomer. © 1997 Elsevier Science Ltd.

Because of our interest in the study of solvent-free phase transfer catalysis[1] as a means of performing asymmetric reactions, and due to the many reports in this field,[2] we decided to investigate the Michael addition of 2-phenylcyclohexanone **1** to chalcone under PTC conditions. The existence of π-moieties in both the enolate and Michael acceptor reactants leads to a new situation in which two different π–π interactions are possible: i) enolate-catalyst, and ii) Michael acceptor-catalyst; providing a model to study which interaction predominates.

In order to find the best conditions for the reaction with chalcone, we firstly performed the reactions with methylvinylketone (MVK) and methyl acrylate using tetrabutylammonium (TBAB) and N-benzylephedrinium bromides as catalyst, and potassium hydroxide as base. Accordingly, the corresponding 2-(3'-oxobutyl)-2-phenylcyclohexanone and methyl 3-(2-oxo-1-phenylcyclohexyl)propionate were obtained, but as racemic mixtures.

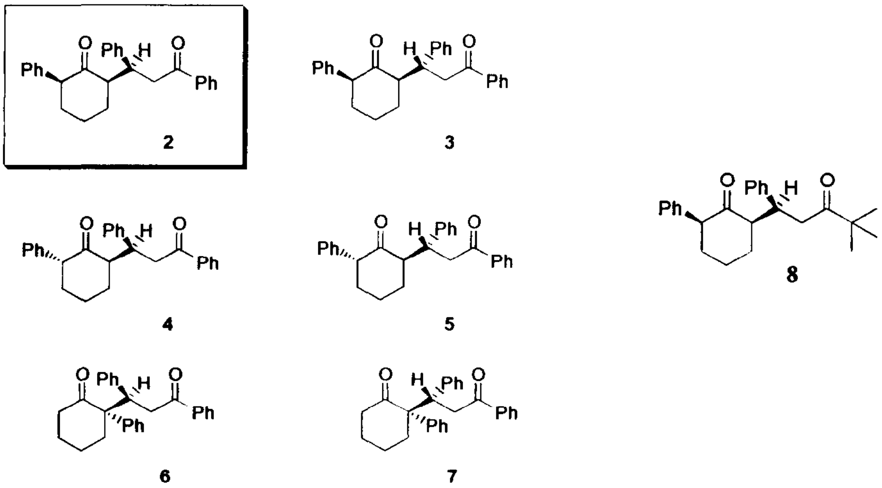
Substituting MVK with chalcone, mixtures of 2-phenyl-2-(1',3'-diphenyl-3'-oxopropyl)cyclohexanone and 2-phenyl-6-(1',3'-diphenyl-3'-oxopropyl)cyclohexanone, henceforth referred to as the 2,2- and 2,6-regioisomers, were unexpectedly obtained. (Table 1)

Table 1. Effect of the phase transfer agent. (base, KOH; t, 24h)

Q^+	T (°C)	yield (%)	2,2-	2,6-	2,2- / 2,6- ratio
TBAB	20	42	25	17	60 / 40
Ephedrinium	20	48	35	17	73 / 20
TBAB	60	49	8	41	16 / 84
Ephedrinium	60	42	16	26	40 / 60

The 2,2-regioisomer was favoured when ephedrinium salt was used instead of TBAB. The 2,2-regioisomer is formed from the thermodynamic enolate, which leads to a crowded transition state, while the 2,6 regioisomer is formed from the kinetic enolate, through a less crowded transition state. The obtained results show the preference for the thermodynamic enolate, using the ephedrinium salt as catalyst, probably as a result of the stabilisation of the enolate through a π–π interaction between the catalyst and the enolate. It can be concluded that the catalyst-enolate interaction predominates over the catalyst-Michael acceptor interaction and this interaction is responsible of the regioselectivity obtained.

After careful separation by column chromatography, six products were identified: the four diastereoisomers of the 2,6-regiosomer (**2**, **3**, **4** and **5**) and the two diastereoisomers of the 2,2-regiosomer (**6** and **7**) (Scheme 1).



Scheme 1

In the case of the unexpected 2,6-regioisomer one of them was predominant. From NMR experiments and molecular mechanics the structure of this prevailing isomer was determined to be (2S,6R,1'S)-2-phenyl-6-

(1',3'-diphenyl-3'-oxopropyl)cyclohexanone **2**.[3] In the case of the 2,2-regioisomer compound **7**, (2S,1'R)-2-phenyl-2-(1',3'-diphenyl-3'-oxopropyl)cyclohexanone, was predominant. (Table 2)

Table 2.

Q^+	T (°C)	yield	2,2- / 2,6- ratio	**2** / **3** / **4** / **5** ratio	**6** / **7**ratio
TBAB	20	42	60 / 40	57 / 7 / 17 / 17	37 / 63
Ephedrinium	20	47	73 / 20	42 / 10 / 26 / 23	49/ 51
TBAB	60	49	16 / 84	41 / 28 / 16 /15	30 /70
Ephedrinium	60	42	40 / 60	62 / 8 / 11 / 18	33 / 67

The effect of the ephedrinium salt, which favours the 2,2-regioisomer was then examined and a new reaction was performed in which this salt was replaced with TBAB as catalyst and potassium *tert*butoxide as base. As a result, compound **2** was obtained in 76% yield (99% *de*).[6] No catalysed reaction afforded lower yield. A similar result was obtained using 4,4-dimethyl-1-phenyl-1-penten-3-one. In this case the 2,6-regioisomer was obtained in 68% yield, with the (2S, 6R, 1'S) diastereoisomer **8** predominating (*de* >99%). Reactions with other α,β-unsaturated carbonyl compounds such as 4,4-dimethyl-1-phenyl-3-penten-1-one and methyl cinnamate were performed but no reactions were observed under the standard reaction conditions.

Based on literature reports about diastereoselective Michael additions,[4] we tested the effect of the counterion and a new set of reactions with chalcone **1** and various cations were performed.[5] The results are summarised in Table 3.

Table 3. Effect of the cation on diastereoselectivity.

entry	base	overall yield	*de* (**2**)	2,2-/2,6 ratio
1	$LiOBu^t$	49	74	8/92
2	NaOH	47	48	11/89
3	KOH	42	22	40/60

Q^+, N-benzylephedrinium bromide; T=60°C; t=24h.

As Table 3 shows diastereoselectivity significantly varies with the counterion, the ratio of diastereoisomer **2** increasing as we go from potassium to lithium. This result suggests a TS with participation of the metal ion. A possible transition state for this reaction is represented in Figure 2. The main feature of this proposed TS is the all-equatorial arrangement of the phenyl groups. The approaches for the other diastereoisomers necessarily place one or two phenyl groups in axial disposition. A more coordinating cation, as Li^+, enhances the differences of energy between the transition states.

In conclusion, the Michael addition of 2-phenylcyclohexanone to bulky α,β-unsaturated ketones mainly leads to the 2,6-regioisomer. This result *a priori* unexpected, indicates that the reaction is kinetically controlled and the thermodynamic enolate is disfavoured because of the highly hindered approach of the bulky group. The predominance of a enolate-catalyst interaction over Michael acceptor-catalyst interaction is showed. A transition state involving the participation of the metal ion is suggested in order to explain the observed diastereoselectivity. Careful choice of the reaction conditions (catalyst, base and metal ion)[6] yields high diastereomeric excesses (up to 99%) together with high regioselectivity.

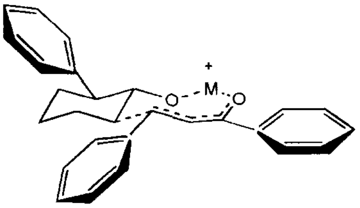


Figure 2

Work aimed at finding reaction conditions to enhance enantioselectivity is in progress.

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REFERENCES

1. Bram, G.; Loupy, A.; Sansoulet, J. *Isr. J. Chem*, **1985**, *26*, 291.
2. a) Dolling, U. H.; Davis, P.; Grabowski, J. J. *J. Am. Chem. Soc.*, **1984,** *106*, 446. b) O'Donnell, M. J.; Bennett, W. D.; Wu, S. *J. Am. Chem. Soc.*, **1989,** *111*, 2353. c) Loupy, A.; Zaparucha, A. *Tetrahedron Lett.* **1993,** *34*, 473.
3. Data for compounds **2** and **8**. Compound **2,** ^{1}H-NMR ($DCCl_3$, δ): 1.32 (1H), 1.77 (3H), 1.97 (1H), 2.26 (1H), 2.94 (1H), 3.12 (1H), 3.60 (1H), 3.69 (1H), 3.75 (1H), 7.12 (2H), 7.22 (2H), 7.24-7.31 (6H), 7.37 (2H), 7.48 (1H), 7.88 (2H). ^{13}C-NMR ($DCCl_3$, δ): 25.81, 34.50, 37.35, 41.90, 44.35, 56.16, 58.63, 126.55, 127.04, 128.17, 128.24, 128.32, 128.37, 128.39, 128.76, 132.59, 136.99, 138.19, 141.87, 198.93, 211.02. Compound **8,** ^{1}H-NMR ($DCCl_3$, δ): 0.89 (9H), 1.33 (1H), 1.78 (3H), 1.96 (1H), 2.27 (1H), 2.85 (1H), 2.91 (1H), 2.96 (1H), 3.58 (1H), 3.71 (1H), 7.13-7.38 (10H). ^{13}C-NMR ($DCCl_3$, δ): 25.831, 25.97, 34.51, 37.44, 40.81, 41.71, 43.90, 55.39, 58.60, 126.23, 126.94, 128.18, 128.21, 128.47, 128.79, 138.32, 142.90, 210.75, 213.52.
4. Ouvrad N.; Rodríguez J.; Santelli M. *Angew. Chem., Int. Ed. Engl.*, **1992,** *31*, 1651.
5. General procedure. A mixture of 2-phenylcyclohexanone (1.5 mmol), base (6% mol) and catalyst (6% mol) was stirred for 5 minutes. The Michael acceptor (1.5 mmol) was then added and the reaction mixture was kept at 60°C for 24 hours. The crude mixture was extracted with dichloromethane (20 mL) and filtered. Removal of solvent and column chromatography yielded the pure products.
6. Reaction conditions for the preparation of **2**: A mixture of 2-phenylcyclohexanone (1.5 mmol), potassium tertbutoxide (6% mol) and TBAB (6% mol) was stirred for 5 minutes. Chalcone (1.5 mmol) was then added and the reaction mixture was kept at 60°C for 24 hours.

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